Biocements having improved compressive strength

The prior German Patent Application P 198 13 614.5 relates to biodegradable calcium phosphate cements, in particular mixtures of calcium phosphate-containing powders of different stoichiometric composition having improved properties. These mixtures all comprise tricalcium phosphate (TCP) and one or more other phosphate-containing inorganic compounds of different composition, the TCP content being present in a well-defined particle size range. Essential for the invention was the fact that a specific fraction of fine particles (about 1 - 40 µm) and very fine particles (0.1 - 1 µm) must be present in addition to a specific fraction of coarse particles (40 - 300 µm).

A teaching of the present invention is based on the object of further improving biodegradable calcium phosphate cements of the type described. Here, the following considerations are particularly important:
Up to the end of 1997, only prototypes of biocement D (for composition, cf. DE 19813614.5) were known. Characteristic of these prototypes were their adequate properties with respect to miscibility, cohesion time, dough time and initial and final hardening time according to ASTM C266, but the compressive strength never reached values greater than 50 MPa. It was thus only in the region of trabecular human bone (Driessens et al., Bioceramics 10 (1997) 279-282). Commercial TCP was used as the crystallization nucleus (cf. DE 19813614.5).

An object of the present invention is to achieve biocements having compressive strengths > 50 MPa, which are even in the region of the cortical bone with respect to strength, without these biocements exhibiting adverse changes with regard to processing times and cohesion.

Upon further study of the specification and

appended claims, further objects and advantages of this invention will become apparent to those skilled in the art.

This and other objects are achieved, according to the invention, by using a specially prepared, precipitated hydroxylapatite (PHA), this serving as a crystallization nucleus or nucleating agent for the formation of the carbonized apatite, formed during the hardening reaction, from biocement D. Surprisingly, it is thus possible to achieve compressive strengths of 70 - 80 MPa after the hardening (cf. Tab. 1 and Fig. 1).

An aspect of the present invention thus relates to a mixture of powders which are suitable for the preparation of absorbable calcium phosphate cements, comprising tricalcium phosphate (TCP) in which about 30 - 70% of the TCP particles have a particle size of about 0.1 - 7 µm and about 10 - 60% have a particle size of about 40 - 100 µm, precipitated hydroxylapatite (PHA) and at least one further other phosphate-containing inorganic compound, the PHA being a cation-deficient hydroxylapatite having the composition

$$Ca_{8.75}V(Ca)_{1.25}[(HPO_4)_{5.5-x}(CO_3)_{0.5}](OH)_xV(OH)_{2-x}$$

with values for x between 0 and 2.

It was found that the precipitate formed during the setting and hardening phase from biocement D is a carbonized cation-deficient hydroxylapatite of the above-mentioned empirical formula. V(Ca) and V(OH) are Ca and OH voids in the crystal lattice. The values for x depend in turn on the structurally related water content of the apatite. It was furthermore found that the structure and composition of the PHA used to date as a nucleus for the preparation of the biocement D prototype, the so-called TCP, differs considerably from those of the cation-deficient hydroxylapatite described above. The TCP used in the prior art (cf. DE 198 13614) comprises, as the main phase, apatite which however comprises very little carbonate (CO_2 content < 0.2%)

and, as secondary phases, monetite. This led to the conclusion that it is necessary to prepare a more highly carbonized, precipitated cation-deficient hydroxylapatite which has a structure similar to that established during the setting and hardening of the biocement D. The preferred CO_2 content for the TCP of the present invention is about 0.2 to 10%. Such a material should be more suitable as a nucleating agent for the reaction of the biocement D. The preparation of the PHA is most simply carried out by conversion of three salts according to the following reaction:

$$8.25\ CaSO_4 \cdot 2H_2O + 5.5\ Na_3PO_4 \cdot 12H_2O + 0.5\ CaCO_3 \rightarrow$$

$$Ca_{8.75}V(Ca)_{1.25}[(HPO_4)_{5.5-x}(CO_3)_{0.5}](OH)_xV(OH)_{2-x} + 8.25\ Na_2SO_4 + (82.5-x)\ H_2O$$

Instead of the $CaSO_4 \cdot 2H_2O$, other calcium salts of strong acids, such as, for example, an anhydrate or hydrate of calcium chloride or calcium nitrate, can also be used. However, the disadvantage thereof is the high deviation from stoichiometry, so that it is not possible to predict with certainty how much calcium is contained proportionately in the three salts.

In order to obtain a cation-deficient hydroxylapatite, the solution should have a pH between about 7 and 9, preferably between about 7 and 8. This is best achieved by dissolving Na_2HPO_4 or K_2HPO_4 or NaH_2PO_4 or KH_2PO_4 or a mixture thereof in an aqueous solution, in which the three above-mentioned salts are then correspondingly dissolved. The primary salts of phosphoric acid additionally have the advantage that they liberate CO_2 from the $CaCO_3$ of the biocement D powder mixture and thus enlarge or increase its porosity, which makes it possible to increase the remodelling rate.

A further precondition is the particle size of the PHA. In order for it to be suitable as a nucleating agent in biocement D, H or F (cf. DE 19813614.5), the

particle size should be between about 0.5 and 10 µm, preferably between about 0.5 and 5 µm. This is achieved by dissolving magnesium chloride and/or magnesium sulfate and/or magnesium nitrate and/or one or more of their hydrates in an aqueous solution in which the reaction to give the PHA is carried out and in which the magnesium salts are dissolved, preferably before the three salts according to the above-mentioned equation are mixed in. The precipitate of PHA in the solution should be stored for a relatively long time at room temperature in order to complete the incorporation of the carbonate anions into the PHA. In order to avoid crystal growth of the precipitate increases in temperature should be avoided. Thereafter, the precipitate is removed from the aqueous solution, for example by filtration or centrifuging, the precipitate being washed with an excess of an aqueous solution comprising a neutral electrolyte, in order to remove sodium and sulfate ions. Traces of these ions in the PHA of the order of magnitude of about < 0.1% by weight are acceptable. Preferably Na or K salts, in the form of chlorides and/or sulfates and/or nitrates and/or one or more of their hydrates, are used as neutral electrolytes. The reason for using these neutral electrolytes in the wash solution is to prevent the swelling and the disproportionation of the precipitate. After washing of the precipitate, it is dried overnight at about 120°C. In order to avoid aggregation, the drying should not be carried out for more than 16 h. The PHA thus prepared is then ready for use for the preparation of the final biocement D powder.

The PHA according to the invention can be used not only for the preparation of biocement D but also for the preparation of cement mixtures F and H. The compositions and mixing ratios of the biocements D, F and H are disclosed in WO 99/49906. As already mentioned above, however, a PHA of a different composition was used in these biocements.

In a preferred embodiment, the content of PHA

is about 1 to 5% by weight, based on the total dry mass. More preferably, the PHA content is about 1.7 to 2.7% by weight, based on the total dry mass of the biocement.

Suitable compounds which can be mixed with TCP are in general all inorganic compounds which comprise calcium and phosphate. The compounds which are selected from the following group are preferred:
$CaHPO_4$, carbonate-containing apatite and $CaCO_3$.

The mixtures according to the invention can, if desired, also comprise known setting accelerators. Disodium hydrogen phosphate is preferred here.

Furthermore, it is desirable to mix with the mixture pharmaceutical active ingredients which have a very wide range of actions. Examples of such active ingredients are growth factors, such as FGF (Fibroblast Growth Factor), BMP (Bone Morphogenetic Protein), a growth factor from the TGF-β super family, TGF-ß (Tissue Growth Factor), or other active ingredients, such as prostaglandins. Owing to their structure, the biocements are capable of releasing the active ingredients into the environment within a few days after the implantation.
Furthermore, it is useful to add antibiotics or disinfectants to the mixture according to the invention, as temporary protection from population with germs during the implantation, analogously to the known mixtures according to WO 99/49906.

The invention also relates to a corresponding mixture in the form of an aqueous solution, paste or suspension and its use for the preparation of biodegradable implantable synthetic bone materials.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius; and, unless otherwise indicated, all parts and percentages are by weight.

The entire disclosure of all applications, patents and publications, cited above and below, and of

corresponding European Application No. 00110045.2, filed 12 May 2000 is hereby incorporated by reference.

The PHA is prepared according to the following example.

Example:

Three salts are combined in the following amounts and homogeneously mixed.

40.67 g of $CaSO_4 \cdot 2H_2O$ + 60.0 g of $Na_3PO_4 \cdot 12H_2O$ + 0.96 g of $CaCO_3$

This mixture is transferred to a 600 ml beaker. 200 ml of an aqueous solution consisting of 20 g of $Na_2HPO_4 \cdot 2H_2O$ + 5 g of $MgCl_2 \cdot 6H_2O$ + 20 g of K_2HPO_4 per 1 000 ml are then added. The solution is stirred at room temperature for 2 h. The precipitate is separated from the solution by means of filtration. The precipitate is then washed 20 times with, in each case, 50 ml of a 0.9% NaCl solution. Drying of the precipitate is then carried out overnight at 120°C. No aggregation is observed. The X-ray diffraction pattern indicated the structure of a microapatite. The FT-IR spectrum showed characteristic apatite and carbonate bonds of the B type.

Tab. 1 shows the compressive strength (in MPa) of the present invention after 2, 4, 6, 18, 72 and 240 hours in comparison with WO 99/49906 (biocement D).

Tab. 1

Time [h]	Compressive strength WO 99/49906 (Biocement D)	Compressive strength Invention
2	16	
4	26	
6		29.2
18	45	46
72	47	74.3
240	48	75.5

Figure 1 shows the values from table 1 graphically.

The results show that the object of the invention is achieved and the compressive strength of the PHA according to the invention after about 48 h has substantially higher values compared with the prior art.

The compressive strength was determined using a Lloyd material tester of the type LR50K after immersion for 2, 4, 6, 18, 72 and 240 hours in Ringer's solution. The reaction product is determined by means of X-ray diffractometry.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.